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Review

Prognostic and clinicopathological significance of CapG in various cancers: Evidence from a meta-analysis

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ABSTRACT

Background: The gelsolin-like actin-capping protein (CapG) is an actin-binding protein in the gelsolin superfamily. Increasing evidence indicates that CapG is highly expressed in various types of cancer. However, the role of CapG in malignant tumors is still controversial. Therefore, we conducted a meta-analysis to assess the prognostic value and clinicopathological significance of CapG in malignant tumors.

Method: We searched for eligible studies in the PubMed, Web of Science, Embase, and Cochrane databases. Stata SE12.0 software was used for quantitative meta-analysis. The hazard ratios (HRs) and odds ratios (ORs) with 95% CI were pooled to assess the relationship between CapG expression and overall survival (OS), as well as clinicopathological parameters.

Results: Sixteen studies with a total of 1987 cancer patients were included in this meta-analysis. The results showed that higher CapG expression was statistically correlated with shorter OS (HR 1.70, 95% CI 1.43–1.97, $P < 0.001$), positive lymph node metastasis (OR 1.91, 95% CI 1.19–3.09, $P = 0.008$), advanced TNM stage (OR 1.87, 95% CI 1.17–3.00, $P = 0.009$), advanced T-primary stage (OR 2.54, 95% CI 1.08–6.00, $P = 0.033$) and male sex (OR 1.77, 95% CI 1.23–2.56, $P = 0.002$). However, no significant correlation was observed between increased CapG expression and advanced age, larger tumor size, differentiation, or advanced histopathologic grading ($P > 0.05$).

Conclusions: High CapG expression is associated with a poor prognosis and worse clinicopathological parameters in various cancers. CapG is a potential prognostic biomarker and a possible clinicopathological predictive factor for various cancers.

1. Introduction

Cancer is one of the leading causes of death worldwide. It is estimated that 8.2 million deaths were caused by cancer in 2012, and this number is still rising [1]. According to a recent study by the American Cancer Society, the United States will have about 1,762,450 new cancer cases and 606,880 cancer-related deaths cases in 2019 [2]. Despite significant advances in diagnostics and improved healthcare, the prognosis of cancer patients remains unsatisfactory. Biomarkers can be used to effectively assess tumor diagnosis and prognosis, and their important role in various cancers has been widely demonstrated. Therefore, reliable and effective biomarkers are urgently needed to help doctors make early clinical decisions and predict the clinical outcomes of cancer patients.

Macrophage capping protein (CapG), which shows partial homology to the N-terminus of gelsolin, was first isolated from alveolar macrophages [3]. As a member of the gelsolin family, it is found in the cytoplasm and nucleus [4]. CapG was found to be highly expressed in macrophages [5]. The biological activities of CapG include macrophage movement, membrane folding, phagocytosis and vesicle sorting [6]. In addition, CapG is involved in the shaping of cytoskeletal filaments by remodeling actin. It regulates actin length and produces propulsion by blocking the end of the filament in a Ca^{2+}-dependent manner [7]. CapG has been shown to be an important regulator of cellular motility in endothelial cells [8] and fibroblasts [7]. Several studies have demonstrated the relationship between CapG and overall survival (OS) as well as the clinicopathological features of cancer patients [9–11]. However, there is still controversy surrounding the prognostic role of CapG

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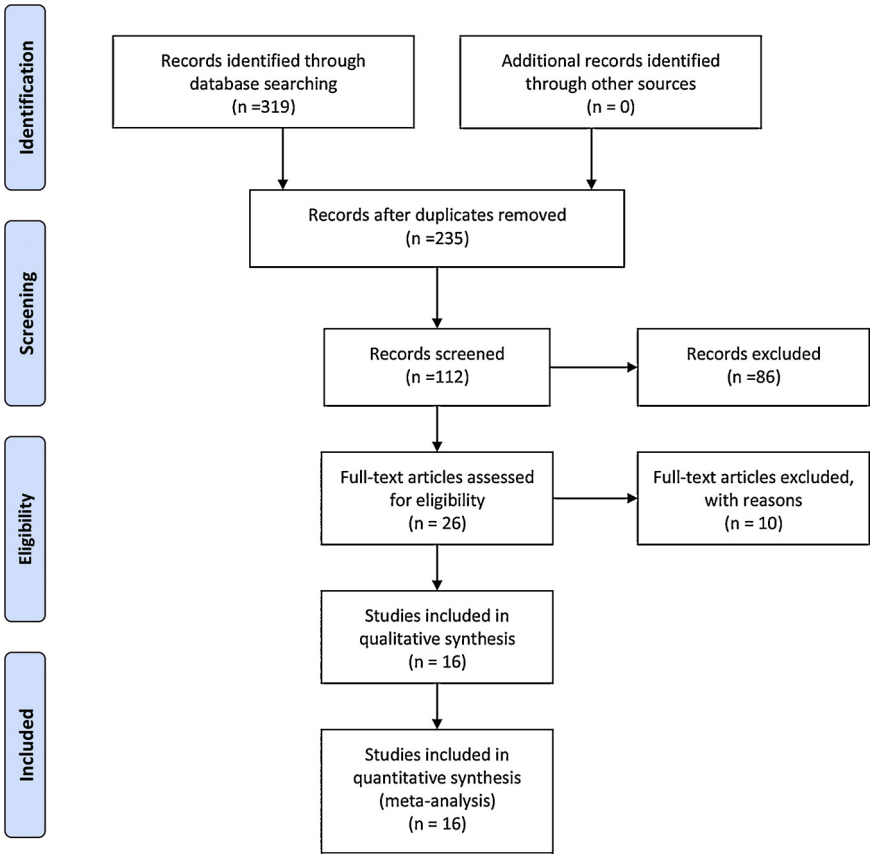

Fig. 1. Flow diagram of the literature retrieval and selection process.

according to the available evidence. In this meta-analysis, we systematically collected the published evidence of the relationship between CapG and overall survival (OS) as well as the clinicopathological features of cancer patients.

2. Materials and methods

2.1. Literature search strategy

The studies included in this meta-analysis were obtained through systematic computer literature searches. We searched for keywords in different databases for reports, including the PubMed, Web of Science, Embase and Cochrane electronic databases. We used the MeSH terms “CapG”, “capping actin protein”, “gelsolin like”, “macrophage capping protein”, “cancer”, “tumor”, “neoplasm” and “carcinoma” in combination with keywords. In addition, we manually searched the reference lists of all articles that may qualify for additional relevant publications. The included studies were published before the cut-off date of March 1, 2019.

2.2. Inclusion and exclusion criteria

Eligible studies were enrolled in this meta-analysis according to the following criteria: (1) research on all types of human cancer; (2) the expression levels of CapG in tissue specimens were determined; (3) information of the associations between CapG expression and prognosis or clinicopathological parameters; and (4) reported odds ratios (ORs) for pathological features or hazard ratios (HRs) with 95% CI or provided sufficient data to estimate them in relation to the CapG expression. Exclusion criteria were: (1) research without suitable data; (2) overlapping data; (3) reviews, case reports, letters, animal studies or expert opinions; or (4) articles from which it was not possible to extract or calculate raw data.

2.3. Date extraction

The information and data were extracted by two investigators (Zhiquan Lang and Yuting Chen) independently, and a third investigator (Hanyan Zhu) was used to judge any disagreements. For each study, the following information and data were collected: first author's last name, year of publication, country, total sample size, follow-up time (months), measurement of results, critical value of CapG expression and clinicopathological parameters such as sex, age, lymph node metastasis, T-primary stage, tumor size, and TNM staging. We extracted the results of multivariate analysis for OS from the included studies wherever possible. For studies that only provided overall survival curves, we used Engauge Digitizer version 4.1 to extract the survival data [12].

2.4. Quality assessment

We used the Newcastle-Ottawa Scale (NOS) to evaluate the quality of all included studies [13]. The NOS scores ranged from 0 to 9 and NOS scores $\geq$ 6 were considered to indicate high quality research. This meta-analysis includes only high quality research.

2.5. Statistical methods

We used Stata SE12.0 to conduct the statistical analysis of the OS and odds ratios (ORs) of the clinicopathological parameters related to OS. The random effects model was used to pool studies with significant heterogeneity, as determined by the inconsistency index ($I^2 \geq 50\%$) and the chi-squared test ($P \leq 0.10$); otherwise, the fixed effects model was used. We used Begg’s and Egger’s tests to investigate potential

Table 1
Relevant features of the studies included in the meta-analysis.

Author	Year	Country	Cancer type	Sample size	Follow-up (mouths)	TNM stage	Treatment	Outcome measures	Analysis type	Cut-off value	NOS score
Partheen [19]	2008	Sweden	OC	43	over 150	43(III)	surgery	OS	U	NR	6
Xing [25]	2016	China	Glioma	90	over 10	9/28/22/31 (I/II/III/IV)	NR	OS	U	Score > 8	6
Li [15]	2016	China	PC	76	over 60	NR	surgery	OS	M	Score ≥4	7
Morofuji [17]	2012	Japan	ICC& ECC	196	over 180	NR	surgery	OS	M	Score ≥1+	8
Huang [9]	2018	China	BC	250	over 140	148/57(I-II/III)	surgery	OS	U	NR	8
Zhu [26]	2012	China	LC	121	over 40	77/44(I/II–IV)	surgery	OS	M	Score > 2	7
Yun [11]	2018	China	Glioma	292	over 100	12/108/46/119(I/II/ III/IV)	surgery	OS	M	Score > 3	8
Westbrook [23]	2016	UK	BC	361	over 60	NR	mixed	OS	M	Score ≥ 3	7
Thompson [21]	2007	UK	PCC	69	NR	NR	NR	NR	NR	Score ≥ 2	6
Shao [20]	2011	China	LC	75	NR	44/31(I+II/III+IV)	NR	NR	NR	Score > 6	7
Nomura [14]	2008	China	OSCC	79	NR	4/15/19/41	surgery	NR	NR	Score >78.68	8
TSAI(1) [10]	2018	China	HCC	38	NR	23/15 (I+II/III+IV)	NR	NR	NR	NR	6
TSAI(2) [22]	2018	China	CRC	57	NR	13/26(I+II/III+IV)	NR	NR	NR	Expression index ≧ 1.5	6
Wu [24]	2017	China	CRC	84	NA	41/43(I+II/III+IV)	surgery	NA	NA	Score≥ 6	7
Li [16]	2010	China	NC	66	NR	7/38/21(II/III/IV)	NR	NR	NR	Positive counts > median	6
Mu [18]	2017	China	PC	90	NR	NR	surgery	NA	NR	Positive-staining > 25%	7

NR: not reported; OS: overall survival; NA: not available; OC: ovarian cancer; PC: prostate cancer; ICC&ECC: intrahepatic cholangiocarcinoma and extrahepatic cholangiocarcinoma; BC: breast cancer; PCC: pancreatic cancer; LC: lung Cancer; OSCC: oral squamous-cell carcinoma; HCC: hepatocellular carcinoma; CRC: colorectal cancer; NC: nasopharyngeal carcinoma; U: univariate; M: multivariate.

publication bias. Sensitivity analysis was also performed to assess the stability of the results. A *p*-value of less than 0.05 was considered to indicate statistical significance.

3. Results

3.1. Main features of the included studies

After searching keywords in the PubMed, Web of Science, Embase and Cochrane electronic databases, 235 related studies were identified. However, 219 studies were excluded after screening the headlines, abstracts and data. Finally, 16 studies [9–11,14–26] with a total of 1987 patients (Fig. 1) were included in this meta-analysis. The average sample size was 124, ranging from 43 to 361. Among the 16 included studies, 12 were from China, 1 from Japan, 1 from Sweden and 2 from the UK. Eight studies were used to evaluate the HRs for OS of the cancer patients. We used the Newcastle-Ottawa Scale (NOS) to assess the quality of all included studies [13]. The quality of all studies included in this meta-analysis was high, with NOS values between 6 and 8, and a mean value of 6.875. The main features of the eligible studies are summarized in Table 1.

All studies used tissue samples to measure the expression CapG. All studies tested CapG expression levels using the same test method - immunohistochemistry. Only 3 studies [9,10,19] failed to report the details of cut-off values. Most studies indicated that patients were not exposed to radiation or chemotherapy prior to surgery [9,15,17–19,23–26], but several did not clearly report whether other therapies including adjuvant chemotherapy and radiation therapy were administered before surgery.

3.2. Association between CapG levels and OS

Among the 16 eligible articles [9–11,14–26], the prognosis of OS according to CapG levels was recorded in 8 studies. A comprehensive analysis of eight studies showed that high expression of CapG is associated with worse OS (pooled HR 1.70, 95% CI 1.43–1.97, $P < 0.001$; Fig. 2). Owing to moderate heterogeneity ($I^2 = 0.0\%$, $P = 0.863$), a fixed effects model was used to pool the HRs. To determine the prognostic role of CapG in different cancers, studies were divided into subgroups by geography. The results indicated that high CapG expression was an unfavorable prognostic indicator in Asia (pooled HR 1.74, 95% CI 1.44–2.04, $P < 0.001$), but not in Europe (pooled HR 1.54, 95% CI 0.92–1.16, $P < 0.001$) (Table 2). After stratification by tumor type, the HRs for the high versus the low CapG expression group were 2.02 (95% CI 1.17–2.86, $P < 0.001$) in studies on cancers of the digestive system and 1.67 (95% CI 1.38–1.95, $P < 0.001$) in other cancer studies. Subgrouping by analysis type showed that elevated CapG expression was significantly associated with shorter OS in univariate analysis (pooled HR 1.70, 95% CI 1.32–2.09, $P < 0.001$) and multivariate analysis (pooled HR 1.70, 95% CI 1.32–2.08, $P < 0.001$) (Table 2).

3.3. Associations between CapG levels and clinicopathological parameters

In the 16 included studies, information on the clinicopathological parameters of the cancer patients was reported as pooled ORs and 95% CI (Table 3). The meta-analysis indicated that high levels of CapG expression were significantly correlated with positive lymph node metastasis [9,10,14–16,18,20–26](OR 1.91, 95% CI 1.19–3.09, $P = 0.008$; Fig. 3), advanced TNM stage [9–11,14,16,20,22,24,25](OR 1.87, 95% CI 1.17–3.00, $P = 0.009$; Fig. 4), T-primary tumor [10,14–16,18,20,22,23,25](OR 2.54, 95% CI 1.08–6.00, $P = 0.033$; Fig. 5) and male gender [10,14,16,20–22,24,26](OR 1.77, 95% CI 1.23–2.56, $P = 0.002$; Fig. 6). By contrast, no significant correlation was observed between high CapG expression and other clinicopathological parameters, including advanced age [14,20,21,26] (OR 0.65, 95% CI 0.41–1.02, $P = 0.059$; Fig. S1), tumor size [9,21] (OR 1.10, 95% CI 0.63–1.92, $P = 0.738$; Fig. S2), differentiation [10,20,22,24] (OR 0.48, 95% CI 0.22–1.04, $P = 0.064$; Fig. S3) or histopathological grading [16,23,25] (OR 0.60, 95% CI 0.18–1.98, $P = 0.400$; Fig. S4).

3.4. Sensitivity analysis

Sensitivity analysis was used to assess the stability of crude results. The results showed that the conclusions were stable and robust, as the combined HRs were not significantly affected by the removal any individual study (Fig. 7).

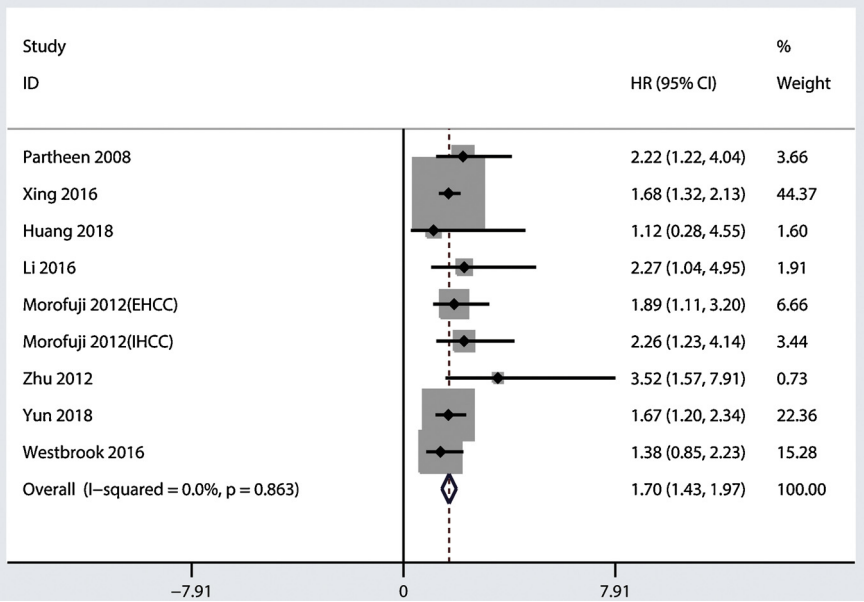

Fig. 2. Meta-analysis of the pooled HRs for the OS of cancer patients.

Table 2
Subgroup analysis of the relationship between CapG overexpression and OS.

OS	Studies (n)	Sample size (n)	HR (95% CI)	Heterogeneity I^2 (%) P_h	Model	*P* value
Overall	8	1423	1.70 1.43-1.97	0.0 0.863	Fixed-effects	< 0.001
Geography						
Europe	2	404	1.54 0.92-1.16	0.0 0.294	Fixed-effects	< 0.001
Asia	6	1019	1.74 1.44-2.04	0.0 0.866	Fixed-effects	< 0.001
Tumor type						
Digestive system	1	196	2.02 1.17-2.86	0.0 0.686	Fixed-effects	< 0.001
Non-digestive system	7	1227	1.67 1.38-1.95	0.0 0.784	Fixed-effects	< 0.001
Analysis type						
Univariate analysis	3	377	1.70 1.32-2.09	0.0 0.665	Fixed-effects	< 0.001
Multivariate analysis	5	1046	1.70 1.32-2.08	0.0 0.998	Fixed-effects	< 0.001

P_h: P Heterogeneity; HR: hazard ratio, CI: confdence interval.

3.5. Publication bias

For the meta-analysis of the association between CapG expression levels and OS, publication bias was tested using Begg's test (Fig. 8). Similarly, Egger's test showed no significant evidence of publication bias ($P = 0.140$).

4. Discussion

As a member of the gelsolin protein family, CapG has been demonstrated to be distributed in the cellular cytoplasm and nucleus [4]. The biological activities of CapG include macrophage motility, membrane ruffling, phagocytosis, and vesicle trafficking [6]. Furthermore, nuclear CapG is associated with the regulation of gene transcription [27,28], and it is considered as a putative oncogene involved in

Table 3
Meta-analysis of the relationship between over-expressed CapG and clinicopathological parameters.

Clinicopathological parameters	Studies (n)	Sample size (n)	OR (95% CI)	Heterogeneity I^2 (%) P_h	Model	*P* value
Gender (Male vs Female)	8	587	1.77 (1.23-2.56)	0.0 0.849	Fixed-effects	0.002
Age (> 60 vs < 60 years)	4	344	0.65 (0.41-1.02)	0.0 0.484	Fixed-effects	0.059
Tumor size (> 2cm vs < 2cm)	2	306	1.10 (0.63-1.92)	10.4 0.291	Fixed-effects	0.738
Lymph node metastasis (Positive vs Negative)	13	1428	1.91 (1.19-3.09)	55.3 0.008	Random-effects	0.008
TNM stage (III + IV vs. I + II)	9	931	1.87 (1.17-3.00)	49.2 0.046	Random-effects	0.009
Differentiation (Well + Moderate vs Poor)	4	218	0.48 (0.22-1.04)	18.9 0.296	Fixed-effects	0.064
T-primary tumor (T3 + T4 vs T1 + T2)	9	908	2.54 (1.08-6.00)	80.7 < 0.001	Random-effects	0.033
Histopathologic grading (I + II vs III + IV)	3	517	0.60 (0.18-1.98)	77.2 0.013	Random-effects	0.400

OR: odds ratio; CI: confidence interval.

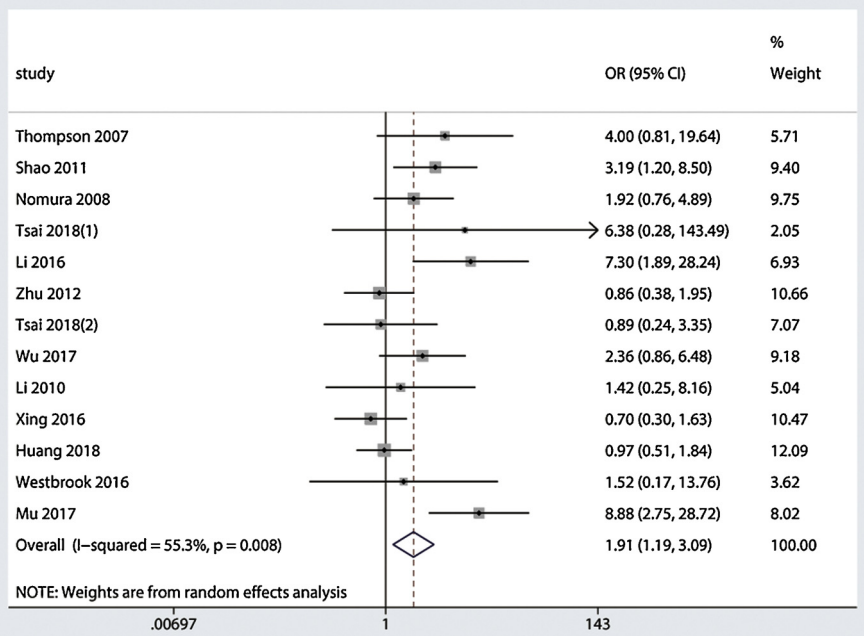

Fig. 3. Meta-analysis of the relationship between CapG overexpression and positive lymph node metastasis.

migration and invasion [29]. According to reports, nuclear complexes are important for migration and invasion, and nucleolar actin may be subject to regulation by actin-binding proteins such as CapG [30,31]. CapG has been shown to be an important regulator of cellular motility in fibroblasts [7] and endothelial cells [8]. Large numbers of studies have shown that CapG has an influence on the invasiveness of cells during tumorigenesis and promotes the metastasis of cancer cells [9–11,14–26,32–35]. High expression of complex biomarkers of CapG and GIPC1 has been reported to be associated not only with the development of bone metastatic breast cancer and reduced survival, but also to predict the therapeutic benefit of the adjuvant zoledronate for reducing bone metastasis [23]. This means that CapG has potential value to forecasting clinical outcomes and the efficacy of therapies.

Cancer is one of the leading causes of death, with poor prognosis worldwide [2]. Determining effective prognostic biomarkers can better inform the clinical decision-making regarding treatment options and outcomes. The overexpression of CapG has been detected in various types of cancer, including gastric [36], pancreatic, lung [20,26], ovarian [19] and other cancers [35,36], as well as glioma [11,25] and hepatocellular carcinoma [10,37]. CapG has been reported to promote tumor invasion and metastasis in tumors or cell lines [29,30,36]. However, the results were inconsistent. The CapG expression levels in the disease-free group were significantly higher than in the recurrence group among patients with stage I lung adenocarcinoma [38]. Furthermore, CapG was suggested to be a tumor suppressor in a study by Watari et al. [33]. However, the mechanisms behind the reported differences are still largely unknown. Moreover, the exact function of CapG in cancer cells is not completely understood. Hence, there are still a series of precise mechanisms that require further exploration and research.

To the best of our knowledge, this is the first meta-analysis to systematically review the prognostic value of CapG in various cancers. We

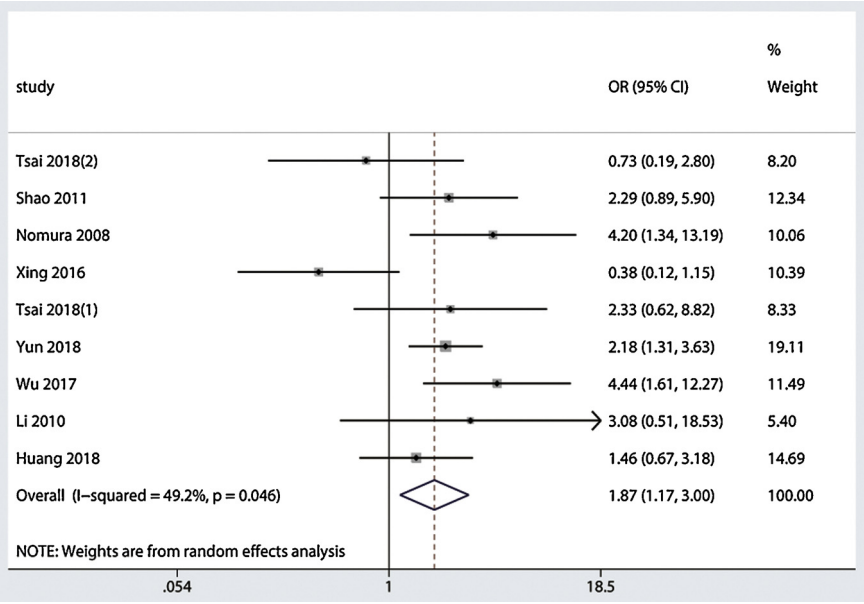

Fig. 4. Meta-analysis of the relationship between CapG overexpression and TNM stage.

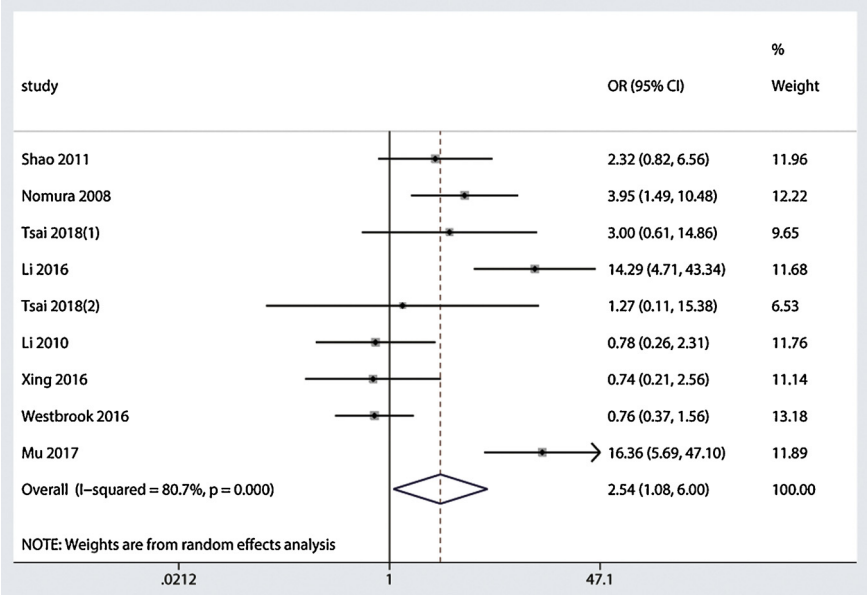

Fig. 5. Meta-analysis of the relationship between CapG overexpression and T-primary tumor status.

conducted this meta-analysis with 16 studies including a total of 1987 cancer patients. By merging data from the included studies, this meta-analysis showed that the high expression of CapG in cancer patients is associated with worse OS (HR 1.70, 95% CI 1.43–1.97, $P < 0.001$). This indicates that high CapG expression is associated with worse prognosis. We also found that high CapG expression is significantly associated with several clinicopathological parameters, including positive lymph node metastasis (OR 1.91, 95% CI 1.19–3.09, $P = 0.008$), advanced TNM stage (OR 1.87, 95% CI 1.17–3.00, $P = 0.009$), advanced T-primary stage (OR 2.54, 95% CI 1.08–6.00, $P = 0.033$) and male gender (OR 1.77, 95% CI 1.23–2.56, $P = 0.002$). However, the pooled data indicated that elevated CapG expression was not significantly linked to advanced age, histopathologic grading and differentiation. These results indicate that CapG may be an important prognostic biomarker for cancer, which could also indicate aggressiveness and progression to metastasis.

Previous studies have reported a potential mechanism for regulating CapG expression, showing that tyrosine kinase [39], hypoxia-inducible factor 1 (HIF-1) [40,41], semaphorin 3A (SEMA3A) [37], integrin 64 [42] and AP-1 [43] lead to upregulation of CapG, which indicates that CapG expression may be related to cancer progression. It was also found that CapG expression affects cell proliferation and apoptosis associated with the Caspase 6/Caspase 9/Bcl-2/p-Akt /Akt signaling pathway [15] and affects tumorigenesis and metastasis by the Hippo pathway resulting in YAP activation [44]. Tonack et al. found that overexpression of CapG in pancreatic cancer cells increases cell motility [45]. In a study by Liao et al, it was demonstrated that inhibition of CapG gene expression in prostate cancer cell lines leads to an obvious reduction in their ability to proliferate, but CapG overexpression alone does not alter the cell cycle dynamics and requires the help of other oncogenes [40]. Huang et al. found that CapG competes with the transcriptional repressor PRMT5 to regulate STC-1 transcription to promote breast cancer metastasis [9]. Taken together, these studies show that CapG has an impact on cancer cell metastasis or on the prognosis of cancer

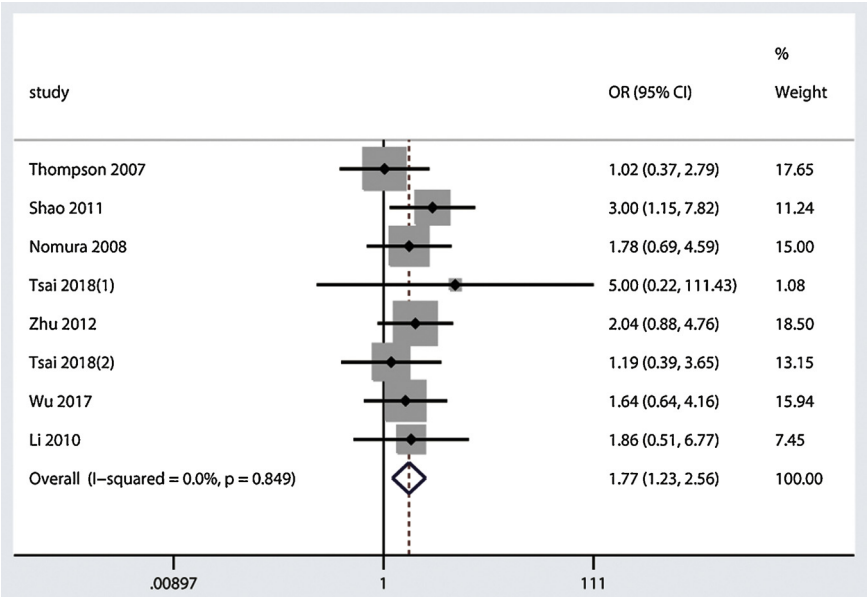

Fig. 6. Meta-analysis of the relationship between CapG overexpression and gender.

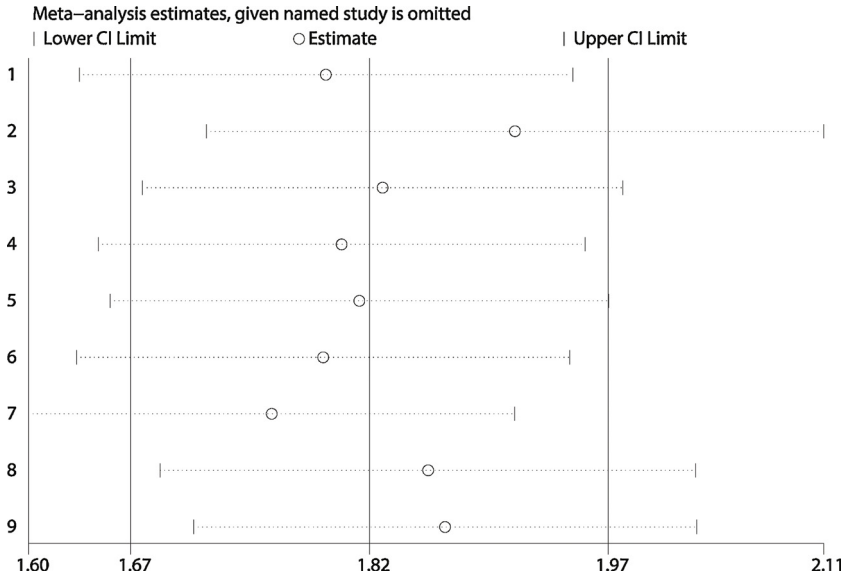

Fig. 7. Sensitivity analyses of studies for OS. CI: confidence interval.

patients, which is consistent with our conclusions.

However, this meta-analysis still has some limitations. First, only 16 studies with a total of 1987 patients were included in this meta-analysis, and its conclusions need to be further confirmed by additional research in the future. Secondly, the IHC criteria used to stratify CapG status varied among the studies, and the cut-off values for high CapG expression were not all consistent. Thirdly, most of the studies included in this meta-analysis were from Asia. Therefore, the data we obtained may be more relevant to Asians than to patients of other ancestry. Fourth, many studies were excluded because they did not meet the inclusion criteria, including some with conflicting results, which may lead to bias in the results of this meta-analysis. Fifth, some of the included studies did not directly provide 95% CIs for the HRs, and some survival data obtained from Kaplan-Meier curves using the Engauge digitizer should be treated with caution. Finally, literature that was not written in English was excluded. Therefore, a larger, multicenter, and higher quality study of CapG expression with a uniform standard for high expression is needed to validate the results of this study.

5. Conclusions

In conclusion, CapG may have some impact on the prognosis of cancer patients. Increased CapG expression may be an important prognostic biomarker for poor OS in various cancers, and appears to be correlated with advanced TNM stage, advanced T-primary tumor stage, male sex and positive lymph node metastasis.

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Declaration of Competing Interest

None of the authors declared any conflict of interest.

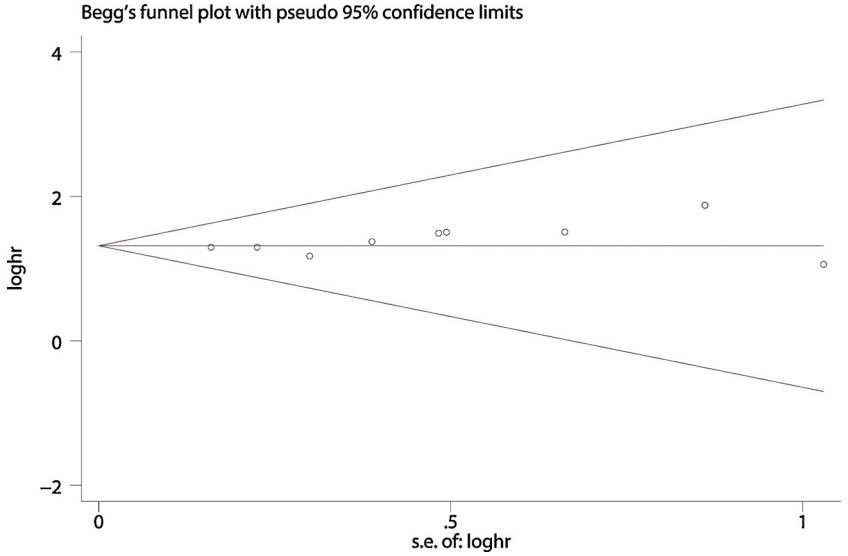

Fig. 8. Funnel plots of publication bias for the correlation between CapG expression and OS.

Acknowledgment

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.prp.2019.152683.

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